REMARKS:

Claim 11 is cancelled without prejudice. New claims 65-67 are added. The subject matter of claims 65-67 is the same as that of the cancelled claim 11. Minor changes are made to the specification. No new matter has been introduced. Claims 1-4, 6, 10, 12-18, and 65-67 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

PRIORITY:

Claims 1-4, 6,10, and 12-18 were afforded the effective filing date of January 6, 1999. The Examiner granted an effective filing date of January 6, 2000 to claim 11, because the Examiner believed that none of the provisional applications references all three monoclonal antibodies. Applicants respectfully disagree.

Claim 11 does not require a simultaneous availability of all three monoclonal antibodies, HUI77, HUIV26, and XL313, as alleged by the Examiner. Instead, claim 11 merely recites alternative types of monoclonal antibodies of the present invention ("...a monoclonal antibody having the binding specificity of monoclonal antibody HUI77, HUIV26, or XL313.") Antibody HUI77 was referenced in the provisional application No. 60,114,877 filed on January 6, 1999. Antibody HUIV26 was referenced in the provisional application No. 60,114,878 filed on January 6, 1999. Antibody XL313 was referenced in the provisional application No. 60,143,534 filed on July 13, 1999 and in the provisional application No. 60,152,496 filed on September 2, 1999. Thus, claim 11 should be afforded the effective filing date of at least July 13, 1999.

Furthermore, in order to simplify assignment of the effective filing date to the subject matter of claim 11, claim 11 is being replaced with new claims 65-67, each claiming a single antibody. Claim 11 is cancelled. Claim 65 is directed to antibody HU177. Claim 66 is directed to antibody HUIV26. Claim 67 is directed to antibody XL313. In accordance with the discussion above, claims 65 and 66 should be

afforded the effective filing date of January 6, 1999 and claim 67 should be afforded the effective filing date of July 13, 1999.

SPECIFICATION:

The specification is objected to because the term "effect" is used instead of the term "affect" on page 3, line 16. Applicants did not find the objected term on page 3 of the specification. Applicants believe that the Examiner's intention was to refer to page 2, line 16, of the specification. Accordingly, applicants made the correction requested by the Examiner on page 2, line 16, of the specification as shown above.

CLAIM REJECTION – 35 U.S.C. §112, FIRST PARAGRAPH:

The Examiner rejected claim 11 as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. This rejection is moot with respect to claim 11 due to the cancellation of the claim. With respect to claims 65-67, which incorporate the subject matter of claim 11, the rejection is traversed.

The specification provides adequate written description and enabling disclosure of the claimed antibodies as it describes methods for producing the antibodies and their specificity. In a recently decided case *Noelle v. Lederman et al.*, (Fed. Cir., 2004) No. 02-1187, the Federal Circuit has summarized the written description requirements with respect to antibodies as follows: "as long as an applicant has disclosed a 'fully characterized antigen,' either by its **structure, formula, chemical name, or physical properties**, or by depositing the protein in a public depository, the applicant can then **claim an antibody by its binding affinity** to that described antigen (*Id.* at page 12, emphasis added). Here, monoclonal antibodies HUI177, HUIV26, and XL313 are claimed by their binding specificity to a particular antigen, a denatured collagen type-I. Since the antigen is

characterized by its chemical name, according to the *Noelle* decision, applicants properly claimed the antibodies. Accordingly, claims 65-67 fully satisfy the written description requirement without a deposit of HUI177, HUIV26, and XL313.

With respect to the lack of enablement rejection, applicants would like to point out that §6 of the Office Action contradicts to the §7 of the Office Action, which acknowledges that the specification is "enabling for the antagonists, designated monoclonal antibodies HUI177, HUIV26, and XL313 binding denatured collagen for the inhibition of angiogenesis." Accordingly, the lack of enablement rejection under §6 is improper and should be withdrawn.

The Examiner maintained the rejection of claims 1-4, 6, and 10-18 under 35 U.S.C. 112, first paragraph, because the specification, while enabling for monoclonal antibodies HUI77, HUIV26, and XL313, allegedly, does not provide enablement for other embodiments of antagonists encompassed by the claims, such as oligonucleotides. The Examiner appears to believe that because the specification provides only examples of three specific antibodies, HUI77, HUIV26, and XL313, inhibiting angiogenesis and because "[a]pplicants have not provided any evidence that suggests that other monoclonal antibodies, polyclonal antibodies, non-peptidic compounds, cyclic peptides or oligonucleotides would have the same inhibitory effect," undue experimentation would be required in order to practice all embodiments of the invention. Applicants respectfully traverse this rejection.

Applicants submit that the specification fully satisfies the requirement for enablement under 35 U.S.C. 112, first paragraph. "The law does not require a specification to be a blueprint in order to satisfy the enablement requirement," *Staehlin v. Secher*, 24 U.S.P.Q. 2d 11513, 1516 (Bd. Pat. App. &Int. 1992). A specification need not describe—and best omits—that which is well known in the art. *See, e.g., In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). It is also well-settled in the law that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in

which the experimentation should proceed." *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982).

Even in the relatively "unpredictable" arts, one need not necessarily disclose how to make each and every embodiment encompassed by the claim. For example, in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976), the court noted that some experimentation is often to be expected in unpredictable areas of technologies. The court further observed that if § 112 required a disclosure of a test with every species covered by a claim in an unpredictable art, then a prohibited number of actual experiments would have to be performed, discouraging the filing of patent applications in unpredictable areas. *Id.*

Instant claims 1-4, 6, and 10-18 are directed to antagonists with specificity to a denatured collagen. The Examiner argues that "[a] number of antibodies may possess a high affinity for the denatured collagens but not be effective in inhibiting angiogenesis." Applicants disagree.

It is discovery of the inventors that antagonists that specifically bind to a denatured collagen with higher affinity than to the native collagen block angiogenesis. Such specificity to a denatured collagen is a sufficient selective criteria that can be used to identify and isolate any type of antagonist claimed in the present invention, including antibodies, oligonucleotides, non-peptidic compounds, and synthetic organic molecules. Thus, the present invention teaches a general method for identification of antagonists based on their higher binding affinity to denatured collagens as compared to the native collagens.

More specifically, the instant specification discloses that the antagonists recognize cryptic epitopes in collagens (page 3, lines 15-18). Since a denaturation of collagens exposes cryptic epitopes, the antagonists of the present invention bind to denatured collagens with higher affinity than to the native collagen (page 15, lines 18-24; page 16, lines 4-16). The specification also discloses that the difference in the binding affinities of antagonists with denatured and native collagens is at least three-fold, preferably 5-fold, and even more preferably 10-fold (page 16, lines 5-16).

Since these general teachings are applicable to any type of antagonists, with some routine screening for antagonists having a higher affinity for denatured collagen than for native collagen, one skilled in the art can identify and isolate all antagonists claimed in the present invention.

Furthermore, the specification explains that a number of conventional screening methods can be used to identify antagonists with specificity for denatured, but not native forms of collagen (pages 16-17). For example, antagonists of the present invention may be identified by a binding assay (page 17, lines 2- 22) and may be further screened by an angiogenesis assay (pages 17-19). Such approaches are discussed in more detail with respect to antagonists that are antibodies (pages 19-24), peptides (pages 24-26), oligonucleotides (pages 26-27), and small organic molecules (page 26, lines 8-13).

Also, the specification provides specific examples of using the general methods and criteria set forth in the instant specification to arrive at, not one, but three antibodies, HUI77, HUIV26, and XL313, having the required specificity for a denatured collagen. Therefore, sufficient and reasonable amount of guidance is given by the specification and it would be only a routine matter for one of skill in the art to conduct screening for other types of antagonists with specificity for denatured collagen. The additional experimentation (screening) that is required to isolate additional types of antagonists is merely routine, not an invitation to research and discover as alleged by the Examiner. Indeed, the instant specification, not the knowledge of one skilled in the art, supplies the novel aspect of an invention -- selection of antagonists capable of inhibiting angiogenesis, wherein the selection is based on antagonist's specific affinity to denatured collagens.

Thus, one skilled in the art would be able to practice the claimed embodiments without undue experimentation in light of the teachings of the instant specification. Consequently, applicants submit that claims 1-4, 6, and 10-18 are enabled by the specification in their full scope and that the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CLAIM REJECTION – 35 U.S.C. §112, SECOND PARAGRAPH:

The Examiner has rejected claims 1-4 and 6-18 under 35 U.S.C. §112, second paragraph on the grounds that the "recitation 'denatured collagens' in claims 1 and 6-9 is vague and indefinite." Applicants respectfully traverse the rejection.

Applicants would like to point out that the Examiner made exactly the same rejection in the Office Action dated October 2, 2001 (§16(a)). The rejection was withdrawn in the Office Action of April 23, 2002 (§7) in view of the applicants' arguments. Thus, applicants believe that the rejection was made in error in the present Office Action. Nevertheless, for the Examiner's reference, applicants include their earlier arguments:

The Examiner's attention is drawn to the following section of the specification discussing "denatured collagens:"

> ***Denatured collagen refers to collagen that has been treated such that it no longer predominantly assumes the native triple helical form.*** Denaturation can be accomplished by heating the collagen. In one embodiment, collagen is denatured by heating for about 15 minutes to about 100°C. Denaturation can also be accomplished by treating the collagen with a chaotropic agent. Suitable chaotropic agents include, for example, guanidinium salts. Denaturation of a collagen can be monitored, for example, by spectroscopic changes in optical properties such as absorbance, circular dichroism or fluorescence of the protein, by nuclear magnetic resonance, by Raman spectroscopy, or by any other suitable technique. Denatured collagen refers to denatured full-length collagens as well as to fragments of collagen. A fragment of collagen can be any collagen sequence shorter than a native collagen sequences. For fragments of collagen with substantial native structure, denaturation can be effected as for a native full-length collagen. Fragments also can be of a size such that they do not possess significant native structure or possess regions without significant native structure of the native triple helical form. Such fragments are denatured all or in part without requiring the use of heat or of a chaotropic agent. The term denatured collagen encompasses proteolyzed collagen. Proteolyzed collagen refers to a collagen that has been fragmented through the action of a protecolytic enzyme. In particular, proteolyzed collagen can be prepared by treating the collagen with a metalloproteinase, such as MMP-1, MMP-2 or MMP-9, or by treating the collagen with a cellular extract containing collagen degrading activity or is that which occurs

naturally at sites of neovascularization in a tissue. (Specification page 14, line 27 to page 15, line 17.)

Therefore, applicants believe that the objected term is clearly defined by the specification.

Also, the Examiner has rejected claims 1-4 and 6-18 under 35 U.S.C. § 112, second paragraph for the recitation of terms "collagen" and "collagens." Applicants respectfully traverse the rejection.

The present invention is directed to antagonists selected by their specificity to denatured collagens over native collagens. Thus, as explained on page 14, lines 20-25, the invention can be used with any collagens, which are broadly defined as extracellular matrix proteins containing a $[Gly\text{-}Xaa\text{-}Xaa]_n$ sequence. Even though the "collagen supper family" includes many collagen types, as pointed out by the Examiner, as long as one can obtain a denatured and a native form of a given collagen, he would be able to practice the instant invention by selecting antigens with a specificity toward the denatured form, as taught by the instant specification.

Accordingly, those skilled in the art will readily recognize that the terms "collagen" and "collagens" refer to compounds of "collagen supper family." Since "a specification need not describe—and best omits—that which is well-known in the art" (See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991)), the objected terms are not indefinite, because a reasonable amount of guidance is given by the specification so that it would be only a routine matter for one of skill in the art to apply the present invention to various types of collagens.

Also, the Examiner has rejected claim 1 under 35 U.S.C. § 112, second paragraph for the recitation of term "substantially reduced affinity." The Examiner appears to believe that the metes and bounds of the claim cannot be determined because "[t]he claim does not clarify what is regarded as limited affinity or what this reduced affinity is compared to." Applicants respectfully traverse the rejection.

The specification defines the term "substantially reduced affinity" on page 16, lines 4-16, of the specification. In particular the specification states:

> A "substantially reduced affinity" is an affinity of about 3-fold lower than that for the denatured collagen, more preferably about 5-fold lower, and even more preferably about 10-fold lower.

Additionally, the claim language specifies that a binding affinity of antagonist to a denatured collagen is compared to a binding affinity of antagonist to a native triple helical form of a collagen. Thus, the term "substantially reduced affinity" is defined by the specification as an affinity, which is at least 3-fold lower than an affinity to which it is compared. Also, the claim language clearly indicates that this reduced affinity of an antigen to native collagen is compared to its affinity to the denatured form of the same collagen.

In view of the above, applicants request a withdrawal of the under Section 112, second paragraph.

CLAIM REJECTION – 35 U.S.C. §102:

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Brooks *et al.*, J. Clin. Invest. 96: 1815-1822, October 1995 (Brooks-95) as evidenced by Brooks *et al.*, Cell 85:683-693, 1996 (Brooks-96). This rejection is respectfully traversed.

The Examiner appears to believe that because monoclonal antibody LM609 interacts with integrin αvβ3 and blocks angiogenesis and because αvβ3 fails to bind native collagen but interacts with proteolyzed collagen, LM609 "would invariably bind denatured collagen type-I and native collagen with reduced affinity." Applicants disagree.

First, with respect to the integrin αvβ3 itself, applicants would like to note that integrins are not encompassed by the amended claim 1. Amended claim 1 of the present invention is directed to antagonists selected from a group consisting of antibodies, non-peptidic compounds, oligonucleotides, and synthetic organic molecules. Thus, peptidic compounds other than antibodies, such as integrin αvβ3, are expressly excluded from the scope of the claim.

Second, with respect to the antibody LM609, its specific affinity is directed to integrin αvβ3 and not denatured collagen, as required by the instant claim 1. There is nothing in Brooks-95 describing antagonists targeting denatured or proteollized collagens. Therefore, Brooks-95 does not explicitly anticipate the instant claim 1.

LM609 does not inherently anticipate the instant claim 1. The most recent inherent anticipation standard articulated by the Federal Circuit in *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373 (Fed.Cir. Aug. 1, 2003), asks whether a prior art device ***necessarily contains*** the omitted feature based on the current knowledge of those skilled in the art. The fact that integrin αvβ3 selectively binds to the denatured collagens and LM609 is specific to the integrin αvβ3 does not necessarily mean that LM609 will selectively bind to the denatured collagen. Biomolecules have numerous binding sites with different affinities and 3-D configurations. The binding site of integrin αvβ3 to the denatured collagen is likely to be completely different from that for binding LM609. Thus, binding of integrin αvβ3 to the denatured collagen and to LM609 does not necessarily mean that LM609 will also bind to denatured collagen with the required specificity. Therefore, Brooks-95 does not anticipate the instant claim 1 as alleged by the Examiner.

Brooks-95 does not make claim 1 obvious. The antagonists of the present invention specifically bind to a denatured collagen with a higher affinity than to the native form of the collagen. The difference in the affinities is at least about 3-fold (page 16, lines 4-16).

Brooks-95, teaches that "**antagonists of integrin αvβ3** [not antagonists of denatured collagen] may provide a novel approach for the treatment of malignant breast tumors" (page 1815, right column, second paragraph). In fact, the specific affinity of monoclonal antibody LM609 referenced by the Examiner is directed to integrin αvβ3 and not denatured collagen. Based on the teachings of Brooks, one skilled in the art would not have attempted to develop antibodies with a specificity to denatured collagen. Therefore, claim 1 is neither anticipated nor rendered obvious by Brooks-95 and Brooks-96. Claims 2-4 and 6 depend, directly or

indirectly, from patentable claim 1 and are, therefore, believed to be patentable for at least the same reasons as claim 1.

Claim 11 is rejected under 35 U.S.C. 102(a) as being anticipated by Petitcleric *et al.* (Cancer Research 59:2724-2730, June 1, 1999). This rejection is moot with respect to claim 11 due to the cancellation of the claim.

The Petitcleric article does not constitute prior art with respect to new claims 65-67. Since the cited reference discloses only antibody HU177, the reference is not relevant with respect to claims 66 and 67 that are directed to different antibodies. The cited reference does not constitute prior art with respect to claims 65, because the effective filing date of claim 65 is January 6, 1999, which is prior to the publication date of the cited reference (June 1, 1999).

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: February 6, 2004

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